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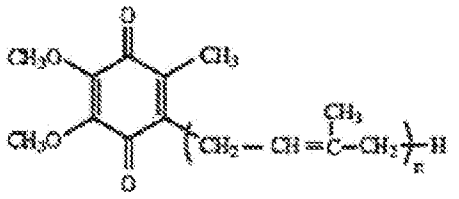
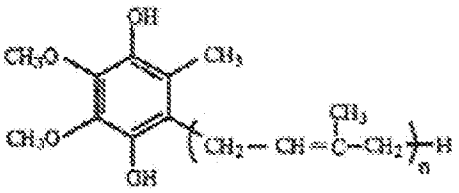
(54) CHOLESTEROL LOWERING AGENT

(57)Abstract:
PROBLEM TO BE SOLVED: To prepare a cholesterol lowering agent having higher safety and excellent cholesterol lowering actions by using a specific coenzyme Q and a specified reduced form coenzyme Q as active ingredients.
SOLUTION: This cholesterol lowering agent contains a coenzyme Q represented by formula I [(n) is 6-11] and a reduced coenzyme Q represented by formula II as active ingredients. The cholesterol lowering agent is useful especially as an agent for hypercholesterolemia, an agent for hyperlipemia and in its turn a therapeutic and preventing agent for arterioslcerosis. A coenzyme Q10 in which (n) is 10 and a reduced coenzyme Q10 are preferred in the compounds represented by formulae I and II. The daily dose of the cholesterol lowering agent for an adult is usually preferably about 100 mg to 10 g.



I



II

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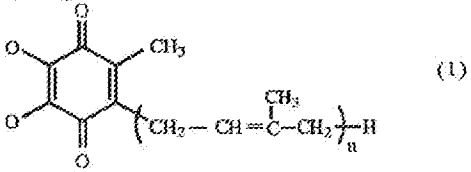
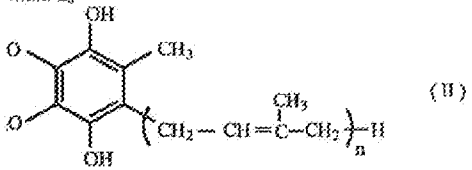
IMS

im(s)]
im 1]A cholesterol lowering agent making into an active principle coenzyme Q expressed with
wing formula (I).
mula 1]



(I)

hows the integer of 6-11 among a formula)
im 2]The cholesterol lowering agent according to claim 1 whose coenzyme Q is coenzyme Q_{10}
se n is 10.
im 3]A cholesterol lowering agent making into an active principle reduction type coenzyme Q
ressed with following formula (II).
mula 2]



(II)

hows the integer of 6-11 among a formula)
im 4]The cholesterol lowering agent according to claim 3 whose reduction type coenzyme Q is
uction type coenzyme Q_{10} whose n is 10.
im 5]The cholesterol lowering agent according to claim 1 or 3 which is an agent for
ercholesterolemia, or an agent for hyperlipidemia.

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TAILED DESCRIPTION

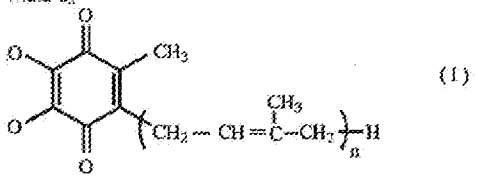
tailed Description of the Invention]

01]

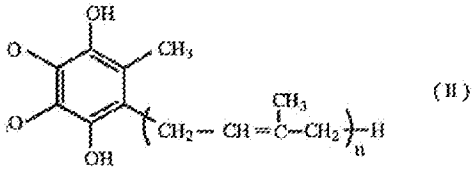
ld of the Invention]This invention relates to the cholesterol lowering agent which makes an active ciple the reduction type coenzyme Q expressed with the coenzyme Q or following formula (II) ressed with following formula (I).

02]

rmula 3]



(I)



(II)

03](n shows the integer of 6-11 among a formula)

related with hypercholesterolemia and hyperlipidemia ****** using the cholesterol lowering agent sh makes an active principle the reduction type coenzyme Q expressed with the coenzyme Q or above-mentioned formula (II) expressed with the above-mentioned formula (I) for the therapy of riosclerosis, and prevention in detail.

04]

scription of the Prior Art]In recent years, the various heart coronary artery systems and brain rial system disease patient accompanying arteriosclerosis or it are increasing by aging of ulation, change of eating habits, etc. There are various factors in generating of arteriosclerosis, rise of the cholesterol amount in blood is especially set to one of the main factors, and it is en clearly that the cholesterol lowering agent in blood is effective in prevention and the therapy rteriosclerosis.

05]As main things of the agent for hyperlipidemia, clofibrate, simfibrate, FIBURATO, such as ofibrate and bezafibrate; Nicotinic acid and nicomol, nicotinic acid derivative [, such as niceritrol,]; lextran sulfate; -- cholestyramine; -- probucol; -- pravastatin. There is a cholesterol lowering nt in blood which makes an active principle 3-hydroxymethyl glutaryl coenzyme A (HMG-CoA) ucing enzyme inhibitor, such as simvastatin and lovastatin, etc. (the work edited by Yutaka ushima and Akimasa Miyamoto, "today's remedy description and manual '97", 419 - 426 pages, koda). Among the cholesterol lowering agents in these blood, what makes it an active principle, ynthetic inhibitor, i.e., HMG-CoA reducing enzyme inhibitor, of cholesterol in the living body, has

received high evaluation clinically by the clear action mechanism and strong drug effect.

[0006]Although these drugs have the operation which reduces the cholesterol amount in blood, it is one side and there is a danger of showing the symptoms of side effects. As side effects of FIBURATO, a hepatopathy, gallstone formation, myositis, ********, rhabdomyolysis, etc. are known, for example. As side effects of a nicotinic acid derivative, a face flush, an exanthema, a headache, vomiting, etc. are known, for example. As side effects of HMG-CoA reducing enzyme inhibitor, a hepatopathy, rhabdomyolysis, a creatine kinase (CPK) rise, diarrhea, abdominal pain, etc. are known as side effects, for example. Also in cholestyramine and probucol which are made for there to be few side effects, a hepatopathy, a CPK rise, etc. are known as side effects.

[0007]There are also many patients of the secondary hyperlipidemia by nephrotic syndrome, an obstructive biliary disease, a hypothyroidism, diabetes mellitus, etc. among hyperlipemic subjects, and there are also many patients having illnesses other than hyperlipidemia among them. After performing alimentary therapy and the kinesitherapy first and observing transition of serum lipid to these patients, it is made good to use the above-mentioned drugs. When an effect is not acquired by administration of 1 agent, action mechanisms differ, and also it can treat by the ability to use an agent together, and a curative effect can be obtained in many cases. Thus, to the patient of hyperlipidemia, two or more drugs are used together in many cases, and a possibility that a drug interaction which is called enhancement of side effects and which is not desirable will be caused in that case increases. For example, in the therapy which uses together FIBURATO and HMG-CoA reducing enzyme inhibitor, the rhabdomyolysis and the acute renal failure accompanying it may be caused.

[0008]By the way, the biosynthesis of cholesterol begins from HMG-CoA being compounded from acetyl CoA and acetoacetyl CoA, HMG-CoA being returned by HMG-CoA reducing enzyme, and mevalonic acid being compounded. The ham A and coenzyme Q which participate in sterol as a cell membrane ingredient, and an electron transport system from mevalonic acid, for example, Dolichol required for sugar protein composition, isopentyladenine used as transfer RNA, important living body metabolite, such as an intracellular messenger and steroid hormone, is compounded. It is called mevalonate pathway (Jay E! Goldstein, em S Brown collaboration, Nature (J. L.Goldstein and M.S.Brown, Nature) 1990, 343 volumes, 425 - 430 pages).

[0009]Since it is rate limiting enzyme which a biosynthesis-of-cholesterol system is comparatively already in the above-mentioned HMG-CoA reducing enzyme, and is located in a stage, HMG-CoA reducing enzyme inhibitor is useful as a cholesterol lowering agent. However, HMG-CoA reducing enzyme inhibitor, such as lovastatin, also inhibiting composition of coenzyme Q (E E! APERUKUISUTO work and a clinical investigator (E. L.Appelkvist et al., Clinical Investigator).) In 1993, 71 volumes, S97-S102 page, and the amount of coenzyme Q in the living body will decrease. As this factor, it is possible that mevalonate pathway is common in the coenzyme Q biosynthesis system and the biosynthesis-of-cholesterol system.

[0010]In order to supply coenzyme Q_{10} which decreased with HMG-CoA reducing enzyme inhibitor to JP,2-233611,A, a means to use coenzyme Q_{10} together to HMG-CoA reducing enzyme inhibitor is indicated.

[0011]Ray em BAL GOSSHI and others (A. M.Bargossi), by using coenzyme Q_{10} together to HMG-CoA reducing enzyme inhibitor has reported the case which barred reduction of coenzyme Q_{10} (molecular ASUPEKUTSU OBU Meidi Soon (Molecular Aspects of Medicine) --- 15 volumes) S187-S193 page, 1994. Namely, in addition to the fall of the cholesterol amount in blood, reduction of the amount of coenzyme Q_{10} in blood is seen by simvastatin independent administration, but. By concomitant use administration of simvastatin and coenzyme Q_{10}, the amount of coenzyme Q_{10} in blood can be raised, without affecting the cholesterol lowering action in blood of simvastatin. However, the concomitant use dose in this case is a dose which compensates the decreasing amount of coenzyme Q_{10}, and does not have on the cholesterol lowering action of base resin.

It is not used as an active principle.

[0012]

[Problem(s) to be Solved by the Invention]In view of the above, safety of this invention is higher

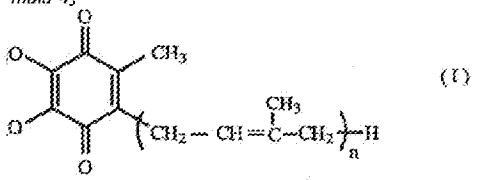
pared with the existing drugs, and agent ****** for the agent for hypercholesterolemia and erlipidemia which has the outstanding cholesterol lowering action aims at providing the therapy preventive of arteriosclerosis.

[3]

ans for Solving the Problem]In order to solve an aforementioned problem, as a result of searching ely a compound which has a cholesterol lowering action, this invention persons found out that uction type coenzyme Q expressed with coenzyme Q and following formula (II) which are ressed with following formula (I) had the operation which reduces a cholesterol amount in blood. resulted in this invention. That is, this invention is following formula (I).;

[4]

rmula 4]

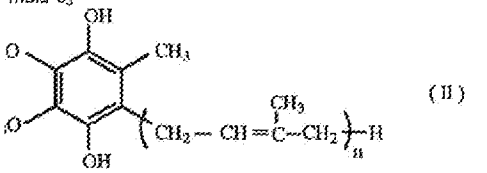


(I)

[5]It is a cholesterol lowering agent which makes an active principle the coenzyme Q expressed (n shows the integer of 6-11 among a formula). This invention is following formula (II) again.;

[6]

rmula 5]



(II)

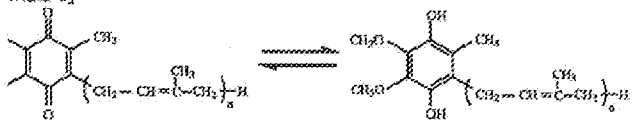
[7]It is also a cholesterol lowering agent which makes an active principle the reduction type nzyme Q expressed with (n shows the integer of 6-11 among a formula). This invention is ained in detail below.

[8]The coenzyme Q expressed with the above-mentioned formula (I) is a physiological ingredient ch exists as an electron transport system constituting factor of the mitochondrion in a cell in the g body, and exists in the living thing from a microorganism to a higher animal widely.

[9]The reduction type coenzyme Q expressed with the above-mentioned formula (II) is changed the coenzyme Q easily expressed by the above-mentioned formula (I) of an oxidation type in the g body, and the coenzyme Q of the above-mentioned oxidation type is conversely changed into a uction type easily in the living body. Therefore, generally a lower type can express coenzyme Q in living body.

[0]

rmula 6]



酸化型補酵素Q　　還元型補酵素Q

[1](n shows the integer of 6-11 among a formula)

known that portion with most coenzyme Q in the living body exists with a reduction type, and the rentage is usually about 40 to 90%.

[2]From reduction type coenzyme Q expressed with coenzyme Q and the above-mentioned nula (II) which are expressed with the above-mentioned formula (I) having a cholesterol lowering

action in blood. The agent ****** for an agent for hypercholesterolemia and hyperlipidemia can use a cholesterol lowering agent which makes an active principle reduction type coenzyme Q expressed with coenzyme Q or the above-mentioned formula (II) expressed with the above-mentioned formula (I) as a therapy and preventive of arteriosclerosis.

[0023]Especially coenzyme Q_{10} and reduction type coenzyme Q_{10} whose n is 10 also in reduction type coenzyme Q expressed with coenzyme Q and the above-mentioned formula (II) which are expressed with the above-mentioned formula (I) are a coenzyme which exists only in Homo sapiens and a higher animal, and are one of the Homo sapiens inside-of-the-body ingredients. In the Homo sapiens blood, it exists in a lipoprotein and not less than 80% is reduction type coenzyme Q_{10} (Takeo Kishi, woods Koichi work, the Vitamin Society of Japan and **, "a dictionary of a vitamin", 402 - 413 pages, Asakura Publishing). As for the above-mentioned coenzyme Q_{10}, since it is used also as a treating agent of congestive heart failure, a nutrient, and a supplement and it is checked conventionally that it is a drug with high safety, it is preferred to use as an active principle of a cholesterol lowering agent in blood of this invention. It is preferred to also use the above-mentioned reduction type coenzyme Q_{10} as an active principle of a cholesterol lowering agent in blood of this invention.

[0024]The above-mentioned cholesterol lowering agent can prescribe [taking orally] it for the patient safely parenterally. It is not limited especially as a pharmaceutical form in the case of administration, but any pharmaceutical forms, such as powder medicine, a tablet, a granule, a capsule, injections, and a suppository, can be chosen.

[0025]When manufacturing the above-mentioned cholesterol lowering agent, addition mixing of other pharmaceutical preparation raw materials permitted pharmaceutically may be suitably carried out with a conventional method. It is not limited especially as such a pharmaceutical preparation raw material, for example, an excipient, disintegrator, lubricant, a binding material, an antioxidant, colorant, a condensation inhibitor, absorption enhancers, a solubilizing agent, a stabilizing agent, etc. are mentioned.

[0026]It is not limited especially as the above-mentioned excipient, for example, sucrose, milk sugar, grape sugar, cornstarch, mannitol, crystalline cellulose, calcium phosphate, calcium sulfate, etc. are mentioned. It is not limited especially as the above-mentioned disintegrator, for example, starch, agar, calcium citrate, calcium carbonate, sodium bicarbonate, dextrin, crystalline cellulose, carboxymethyl cellulose, tragacanth, etc. are mentioned. It is not limited especially as the above-mentioned lubricant, for example, talc, magnesium stearate, a polyethylene glycol, silica, hydrogenated vegetable oil, etc. are mentioned.

[0027]It is not limited especially as the above-mentioned binding material, but For example, ethyl cellulose, methyl cellulose, Hydroxypropylmethylcellulose, tragacanth, a shellac, gelatin, gum arabic, a polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, sorbitol, etc. are mentioned. It is not limited especially as the above-mentioned antioxidant, for example, ascorbic acid, tocopherol, vitamin A, beta-carotene, sodium hydrogen sulfite, sodium subsulfite, sodium pyrosulfite, etc. are mentioned. Especially as the above-mentioned colorant, it is not limited but adding in drugs can use various kinds of things permitted suitably.

[0028]It is not limited especially as the above-mentioned condensation inhibiter, for example, stearic acid, talc, light anhydrous silicic acid, hydrous diacid-ized silicic acid, etc. are mentioned. It is not limited especially as the above-mentioned absorption enhancers, for example, surface-active agents, such as a higher alcohol; higher fatty acid group; glycerine fatty acid ester, etc. are mentioned. It is not limited especially as the above-mentioned solubilizing agent, for example, organic acid, such as fumaric acid, succinic acid, and malic acid, is mentioned. It is not limited especially as the above-mentioned stabilizing agent, for example, benzoic acid, sodium benzoate, ethyl p-hydroxybenzoate, etc. are mentioned.

[0029]A cholesterol lowering agent of this invention can be prescribed for the patient to patients, such as hypercholesterolemia and hyperlipidemia, and can be used for prevention or a therapy of hypercholesterolemia or hyperlipidemia. Therefore, a cholesterol lowering agent of this invention which are an agent for hypercholesterolemia and an agent for hyperlipidemia is also one mode of this invention.

[0030](Direction for use) although a dose of the above-mentioned cholesterol lowering agent changes

· a kind of hypercholesterolemia or hyperlipidemia, and grades — usually — an adult — about 100 ~ 10 g per day are preferred. Actually, compared with a case where it uses together with HMG- ı reducing enzyme inhibitor, it is effective with more doses.

:1]

ımple]Although the example and the example of pharmaceutical preparation of this invention are g up over below and explained to it in more detail, this invention is not limited to these examples.

:2]To an ICR system male mouse (one groups [five]) with an example 1 hypocholesterolaemic-ct weight of around 20g. High cholesterol call acid corrosion food (71.9% standard food, 15% ·ose, 2% salt, 10% coconut oil, 0.6% cholesterol, 0.2% cholic acid, 0.3% choline chloride) was fed ı the 1st day of an examination to the 7th day (free ingestion). Reduction type coenzyme Q_{10} administered orally to the 6th day of an examination, and the 7th day so that it might become mg/kg. Bezafibrate which is commercial antilipemic was administered orally by kg in 50mg /as a ·parison drug. Then, the fast of 24 hours was performed, blood was extracted from the mouse to 8th day of the examination, and the blood serum was separated.

:3]Heparin was made to add and sediment into some extracted blood serums, and heparin mentation lipoprotein was obtained as low density lipoprotein (LDL). the total cholesterol value in ·od serum, and the cholesterol count in LDL — the report (clinical chemistry (Clinical mistry).) of See sheer lines (C. C.Allain et al.) It measured in 1974 according to 20 volumes and ~ 475 pages. The decreasing rate of the total cholesterol in a blood serum and the decreasing of LDL cholesterol were made into the rate which made 100% the control group which has not :cribed drugs for the patient, and it asked for them with the following formula (1).

:4]

:ation 1]

$$\text{率 (\%)} = \left(1 - \frac{\text{投与群のコレステロール値}}{\text{対照群のコレステロール値}}\right) \times 100 \qquad (1)$$

:5]The value which lengthened the LDL cholesterol value from the total cholesterol value in a ·d serum was computed as a high-density-lipoprotein (HDL) cholesterol count. The rate of ease of HDL cholesterol considered it as the rate which made 100% the control group which has prescribed drugs for the patient, and it asked for it with the following formula (2).

:6]

:ation 2]

$$\text{率 (\%)} = \left(\frac{\text{投与群のコレステロール値}}{\text{対照群のコレステロール値}} - 1\right) \times 100 \qquad (2)$$

:7]The result was shown in Table 1. The clear operation which reduces the total cholesterol in a ·d serum was observed in reduction type coenzyme Q_{10} so that clearly from Table 1. . The ·esterol which deposits cholesterol to a blood vessel wall and makes it promote arteriosclerosis ·cially is included. The LDL cholesterol known as what is called the bad cholesterol is reduced arkably. It should take notice of making the HDL cholesterol known as what is called the good ·esterol supposed that arteriosclerosis is prevented increase remarkably including the cholesterol oved from the blood vessel wall.

:8]When bezafibrate and reduction type coenzyme Q_{10} which are the commercial antilipemic ·l as a comparison drug are compared, reduction type coenzyme Q_{10}. Although it was a little ·ior in the fall operation of the determination of total cholesterol in serum, the operation a little ·tanding in the fall operation of LDL cholesterol was shown, and the operation outstanding in the easing action of HDL cholesterol was shown further. The above thing shows that reduction type ·zyme Q_{10} is the outstanding cholesterol lowering agent with high safety.

:9]

·le 1]

	対照群	還元型補酵素Q₁₀	ベザフィブラート
血清総コレステロール (低下率)	325±31mg/dl (0%)	256±37mg/dl (21%)	241±11mg/dl (25%)
LDLコレステロール (低下率)	245±32mg/dl (0%)	180±30mg/dl (25%)	171±10mg/dl (30%)
HDLコレステロール (増加率)	80± 4mg/dl (0%)	98± 4mg/dl (22%)	73± 8mg/dl (−9%)

コレステロール値（mg／dl）は、平均±標準偏差（n＝5）を示す。

[0040]Example of pharmaceutical preparation 1 Powder medicine was manufactured using the manufacture following component of powder medicine. It dried, after dissolving coenzyme Q_{10} in acetone and making this adsorb subsequently to microcrystalline cellulose. This was mixed with amylum maydis and it was considered as the powder medicine which contains 20 mg coenzyme Q_{10} in 200 mg.

Coenzyme Q_{10}10 weight-section microcrystalline cellulose 40 weight-section amylum-maydis 50 weight section [0041]Example of pharmaceutical preparation 2 The tablet was manufactured using the manufacture following component of a tablet. It dried, after dissolving coenzyme Q_{10} in acetone and making this adsorb subsequently to microcrystalline cellulose. Amylum maydis, milk sugar, carboxymethyl cellulose, and magnesium stearate were mixed to this, and, subsequently the solution of the polyvinyl pyrrolidone was granulated with the conventional method as a binding material. After adding talc to this as lubricant and mixing, it tableted to the tablet which contains 20 mg coenzyme Q_{10} in 1 dose.

Coenzyme Q_{10}20 weight-section microcrystalline cellulose 4 weight-section amylum-maydis 25 weight-section milk sugar 15 weight-section carboxymethyl cellulose 10 weight-section magnesium stearate 3 weight-section polyvinyl-pyrrolidone 5 weight-section talc 10 weight section [0042]After granulating the manufacture following component of example of pharmaceutical preparation 3 capsule with a conventional method, the gelatin hard filled capsule was filled up. The capsule which contains 20 mg coenzyme Q_{10} in 1 capsule was obtained.

Coenzyme Q_{10}20 weight-section microcrystalline cellulose 40 weight-section amylum-maydis 20 weight-section milk sugar 62 weight-section magnesium stearate Amount part polyvinyl-pyrrolidone of duplexs 3 weight section [0043]The soft capsule agent was manufactured using the manufacture following component of example of pharmaceutical preparation 4 soft capsule agent. Soybean oil was warmed at 60 **, and coenzyme Q_{10} fused at 60 ** was added, and it dissolved. Vitamin E was added little by little to this, and it presupposed that it is homogeneous, and soft-capsule-ized with the conventional method. The soft capsule agent which contains 20 mg coenzyme Q_{10} in 1 capsule was obtained.

Coenzyme Q_{10}20 weight-section vitamin-E 15 weight-section soybean oil 350 weight section [0044] Example of pharmaceutical preparation 5 Powder medicine was manufactured completely like the example 2 of pharmaceutical preparation except having used coenzyme Q_7 instead of coenzyme Q_{10} of the example 2 of manufacture pharmaceutical preparation of powder medicine.

[0045]Example of pharmaceutical preparation 6 The tablet was manufactured completely like the example 3 of pharmaceutical preparation except having used coenzyme Q_9 instead of coenzyme Q_{10} of the example 3 of manufacture pharmaceutical preparation of a tablet.

[0046]The capsule was manufactured completely like the example 4 of pharmaceutical preparation except having used reduction type coenzyme Q_8 instead of coenzyme Q_{10} of the example 4 of manufacture pharmaceutical preparation of example of pharmaceutical preparation 7 capsule.

[0047]The soft capsule agent was manufactured completely like the example 5 of pharmaceutical

paration except having used reduction type coenzyme Q_{10} instead of coenzyme Q_{10} of the
mple 5 of manufacture pharmaceutical preparation of example of pharmaceutical preparation 8
capsule agent.
8]
ect of the Invention]Since the cholesterol lowering agent of this invention consists of above-
tioned composition, there are few side effects, and they are safe and hypercholesterolemia and
rlipidemia ****** can be used for the therapy and preventive of arteriosclerosis.

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nslation done.]